

Second Supplemental Amendment for Application No. 09/823,088. Applicant(s) MCGINNIS ET AL. 3/5  
August 2, 2004 submitted by fax to 1-703-872-9306

## Remarks

### Regarding the new paragraph that has been requested to be added to the Specification

The new paragraph that has been requested to be added to the Description is subject matter and concepts already in the application. Specifically for example, subject matter is from p. 5 line 15 to p. 6 line 9, of the PCT application, Ann. Hum. Genet. v. 62 (AHG 98) p. 166, and Tables 1 to 3 in AHG 98. This information draws the distinction between the Muller-Myshok and Abel letter and the inventor's calculations and observations regarding the increased power of the TDT and other association tests even when  $m \neq p$  and, or  $\delta \neq \delta_{\max}$  (the more common, less optimal situations) Also p. 10 lines 4 to 12 of the PCT application describes conceptualizing statistical evidence for linkage as occurring in a hump or hump(s), rather than as a sharp "spike" or as falling dramatically from a peak.

Also pp. 12 line 40 to page 13 line 8 of priority application 60/107, 673 describes theory of operation for versions of the invention. This theory notes that it is practical to use the increased power resulting from marker and trait-causing polymorphism (gene) allele frequency similarity. This is because there is a relatively large subrange of marker least common allele frequencies in the vicinity of a trait-causing polymorphism's (gene's) least common allele frequency (when  $m \neq p$ ) with power increased enough to be of practical use to detect evidence for linkage. Whereas the letter of Muller-Myshok and Abel indicates such a subrange of increased power is so very small as to be impractical for use in detecting evidence for linkage. This is because the letter of Muller-Myshok and Abel indicates that the power outside this very small subrange is greatly diminished (and therefore not of practical use when  $m \neq p$ ). Specifically the letter of Muller-Myshok and Abel indicates that the power of association studies such as the TDT can be greatly diminished as soon as the ratio  $m/p$  departs from unity. And again the letter of Muller-Myshok and Abel indicates that the number of necessary families increases dramatically (i.e. dramatically decreased power) as  $p$  differs from  $m$  even when  $\delta = \delta_{\max}$  and also as  $\delta$  decreases.

The application also describes the importance of allele frequency in many places (e.g., p. 41 line 28 of the PCT application). See also AHG 98 p. 168 (top of page) which specifically uses the words "attention to allele frequencies at bi-allelic markers". And this is contrasted with p. 4 line 11 and p. 7 line 18 of the PCT application in which "little attention" is given to marker allele frequency by conventional techniques that are essentially one-dimensional.

Second Supplemental Amendment for Application No. 09/623,068. Applicant(s) MCGINNIS ET AL. 4/5  
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**Regarding words such as "similarity of marker allele frequency and trait-causing polymorphism allele frequency"** in claims such as 103, it is clear that the similarity of marker and trait-causing polymorphism allele frequency includes equality of marker and trait-causing polymorphism allele frequencies. That is, equality is the ultimate form of similarity and is included in similarity; see for example p. 6 lines 3 to 5 and lines 16 to 21 of the PCT application.

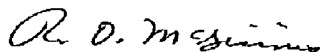
**That Amendment/Response of 6/29/04 was completely responsive to the Examiner's Office Action of December 29, 2003.** As noted in the Amendment/Response of 6/29/04 the basis for the provisional double patenting rejection (based on claims 2, 3 and 4 in Application No. 10/037, 718) has been removed, because these claims (2, 3 and 4 in Application No. 10/037, 718) have been canceled. Point 3) and other points in the Examiner's Office Action of December 29, 2003 deal with Double Patenting Rejections. The Amendment/Response of 6/29/04 specifically discusses point 3 and double patenting. The applicants respectfully submit that the canceling of claims 2, 3 and 4 in Application No. 10/037, 718 is obviously responsive to all the Double Patenting Rejection points in the Office Action.

Second Supplemental Amendment for Application No. 09/623,068. Applicant(s) MCGINNIS ET AL. 5/5  
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### **Conclusion**

In the present Second Supplemental Amendment, applicants have requested the addition of a single new paragraph to the end of the Description. This new paragraph is requested in addition to the paragraphs previously requested to be added to the Specification in the Amendment/Response of 6/29/04 and the First Supplemental Amendment of July 20, 2004. As noted in the Remarks Section, this new paragraph consists of concepts already in the application and is not new matter. A few additional remarks are also included

Respectfully submitted,



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